PATENT COOPERATION TREATY

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REC'D 24 MAR 2006
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/FI2005/000011	International filing date *(day/month/year)* 11-01-2005	Priority date *(day/month/year)* 28-01-2004
International Patent Classification (IPC) or national classification and IPC See Supplemental Box		
Applicant MACROCRYSTAL OY et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      _____, containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08-08-2005	15-03-2006
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. +46 8 667 72 88	Authorized officer Ida Christensen/MP Telephone No. +46 8 782 25 00

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Cover sheet

International patent classification (IPC)

B01D9/02 (2006.01)
C07K 1/00 (2006.01)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/FI2005/000011

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____,
which is the language of a translation furnished for the purposes of:

☐ international search (Rules 12.3(a) and 23.1(b))

☐ publication of the international application (Rule 12.4(a))

☐ international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the claims:

pages _____ as originally filed/furnished
pages* _____ as amended (together with any statement) under Article 19
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the drawings:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/FI2005/000011

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-11	YES
	Claims		NO
Inventive step (IS)	Claims	1-11	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-11	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The present application relates to a method for crystallisation of proteins and peptides, characterised in that two solutions are mixed together, one of which is an aqueous solution of proteins or peptides and the other is an aqueous polymer solution, wherein the polymer is alginate, dextrin, chitosan or pectin or a hydrolysate or a mixture of any of the said polymers. Upon mixing the two solutions the protein or peptide crystallises permanently. The aim is to produce crystallised proteins which float freely in the polymer solution or continuous uniform gel, which have improved stability and which may be used in medical formulations.

Reference will be made to the following documents cited in the International Search Report:
D1) WO 9955310
D2) EP 0263490
D3) US 20020001619
D4) Pharmaceutical Research, vol 18(11): 1483-1488 (2001), Jen A & Merkle H P.

D1 relates to a process for crystallisation of proteins and stabilised protein crystal formulations. It has been found that proteins may be successfully stored in dry form for long periods of time at ambient or elevated temperatures in crystalline form. Formulations comprising the protein crystals are prepared either by (1) adding ingredients or excipients where necessary to stabilize dried crystals or (2) encapsulating the protein crystals or crystal formulations within a polymeric carrier to produce a composition that contains each crystal and subsequently allows the release of active protein molecules.

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

According to D1, protein crystals may be stored either in the form of suspensions by replacing the mother liquor with a nonaqueous solvent, or in dried solid form. Non-aqueous slurries of crystalline therapeutic proteins are especially useful for subcutaneous delivery. In order to enhance the stability of the crystals, excipients such as hydroxypropyl-p-cyclodextrin may be added to the already crystallised protein in mother liquor. See page 35, line 31 - page 37, line 6; page 88, line 15 - page 89, line 14; page 94, line 1 - page 96, line 28; claims 1, 16, 50, 110 and 116.

D2 describes a sustained-release particulate preparation which comprises a polymeric compound which is capable of being degraded in the body, a pharmacologically active agent (e.g. a protein or a peptide), and a natural high-molecular weight compound of sugar origin (e.g. chitosan, pectin or dextrin). The preparation is prepared by dissolving the polymeric compound, and mixing it with the pharmacologically active agent and an aqueous solution of the compound of sugar origin, followed by stirring in order to obtain a preparation which has fine and uniform particle size. There is no indication in D2 of crystallisation of the pharmacologically active agent (see the claims).

D3 relates to sustained-release compositions comprising a hydrophilic polymer, a biologically active agent, e.g. a protein, and a precipitating agent, wherein the composition is characterised in that the biologically active agent is co-precipitated with the polymer. The polymer is for example alginate (see claims 1-10).

D4 reviews methods of crystallising proteins for use in pharmaceutical formulations.

The cited documents D1-D4 represent the general state of the art. The invention defined in claims 1-11 is not disclosed by any of these documents. The cited prior art does not give any indication that would lead a person skilled in the art to the claimed method of crystallisation of proteins. Therefore, the claimed invention is not obvious to a person skilled in the art.

Accordingly, the invention defined in claims 1-11 is novel and is considered to involve an inventive step. The invention is industrially applicable.